REMARKS

I. STATUS OF THE CLAIMS

Following entry of this amendment, Claims 33, 46-49, 54, and 61-67 will be pending in this application. Claims 32, 34-45, 50-53, and 55-60 are herein canceled without prejudice or disclaimer. Claim 33 is herein amended to eliminate its dependency on a canceled claim, incorporating all limitations of the claim from which it depended (claim 32). Support for this amendment can be found at paragraphs [0020-0027] of the Specification as-published. New claims 61-67 are herein added. Support for this amendment can be found at paragraphs [0082-0145] and [0233-0247] of the Specification as-published. Accordingly, no new matter is added by this amendment.

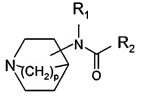
New claims 61-67 are directed to compounds according to claim 33; pharmaceutical compositions comprising at least one compound according to claim 33; methods comprising, *inter alia*, administering at least one compound according to claim 33; and combination products comprising, *inter alia*, at least one first compound according to claim 33. Accordingly, Applicant respectfully submits that new claims 61-67 read on the elected subject matter.

II. REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner rejects claim 54 under 35 U.S.C. § 112, second paragraph, "as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention [according to the Examiner, the] term

'producing' is confusing [and there] is no reaction steps to produce a compound of claim 33 [that] comprises reacting a compound of formula (I)." Office Action at 2.

Applicant respectfully disagrees with the Examiner's characterization of claim 54. Claim 54 recites:

> A process for producing a compound of claim 33, **wherein the process comprises reacting a compound of formula (I)**
>
> 
>
> **(I)**
>
> wherein:
>
> [the different variables of the formula (I) are defined]
>
> **with an alkylating agent of formula R_6-$(CH_2)_n$-A-$(CH_2)_m$-W**, wherein
>
> - W represents a suitable leaving group.

(Emphasis added.)

Applicant respectfully submits that the Examiner's assertion that "[t]here is no reaction steps to produce a compound of claim 33 [that] comprises reacting a compound of formula (I)" is incorrect. Accordingly, Applicant requests that this rejection be withdrawn. As this rejection is the only rejection of record for claim 54, Applicant further submits that claim 54 is now in condition for allowance.

III. REJECTION UNDER 35 U.S.C. § 103

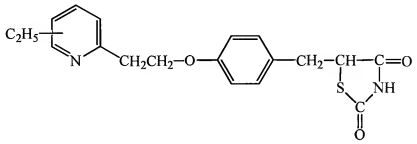
The Examiner rejects claims 33 and 46-49 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sternbach et al., *Journal of the American Chemical Society* (1952), 74, 2219-2221 (hereinafter, "*Sternbach*"). Office Action at 3. The Examiner asserts that *Sternbach* "disclosed [an] analogous compound, which from the STN search is ... Quinuclidine, 3-(2,2-diphenylacetamido)" and that "[t]he difference between the instant claims and the prior art compound is that the instant claims are in the salt form of the prior art compounds." *Id.* at 3-4. The Examiner further alleges that "[a]ll the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention." *Id.* at 4. Applicant respectfully disagrees with the Examiner's characterization of the instant claims and traverses the rejection for at least the reasons that the cited reference fails to suggest the compounds of the invention and the rejection is also inconsistent with the relevant obviousness patent law.

1. The law requires a reason to modify the compounds of the prior art

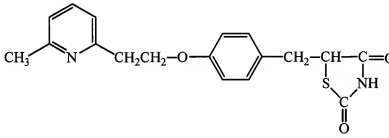
The Examiner's argument seems to imply that compounds structurally homologous to those in the prior art, without more, are *prima facie* obvious. Such is not the standard. Rather, the Federal Circuit has recently indicated that "[i]n addition to structural similarity between the compounds, a prima facie case of obviousness *also requires a showing of 'adequate support in the prior art' for the change in structure*."

Takeda Chemical Ind. Ltd. v. Alphapharm Pty. Ltd., 83 USPQ2d 1169, 1174 (Fed. Cir. 2007) (internal citations omitted, emphasis added).

In *Takeda*, the patented compounds had the general formula (claim 1):



The compound in the prior art, "compound b," had an identical formula to the patented compound, except that a methyl group, instead of an ethyl group, was attached to the pyridyl ring located on the left hand side of the molecule, as indicated in the drawing below. *Id.* at 1172.



"compound b" in *Takeda*

Because the structure of the patented compounds allowed the substitution by the ethyl group on any available carbon atom in the pyridyl ring, the only difference between the prior art compound and the claimed compounds was a methylene group ($-CH_2-$) in

the alkyl radical of the pyridyl ring[1]. The court in *Takeda* held that because there was no motivation to prepare the claimed compounds in light of the prior art compound, the patented compounds were not obvious. *Id.* at 1776-77.

Applicant notes that *Takeda* was decided after the landmark case of *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). Accordingly, the *Takeda* court also considered in its decision the Supreme Court's guidelines enunciated in *KSR* regarding obviousness determinations. *Takeda*, 83 USPQ2d at 1174.

The court additionally commented as follows:

> We elaborated on this requirement [to show adequate support in the prior art for the change in structure] in the case of *In re Deuel*, 51 F.3d 1552, 1558 [34 USPQ2d 1210] (Fed. Cir. 1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.*, an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* **We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required.** *Id.* (citing *In re Jones*, 958 F.2d 347 [21 USPQ2d 1941] (Fed. Cir. 1992); *Dillon*, 919 F.2d 688 [16 USPQ2d 1897] ;

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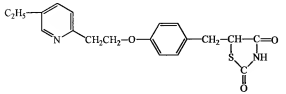
[1] The actual commercial embodiment marketed by the patentee (pioglitazone) was also claimed in a dependent claim, and had the structure shown below. It can be seen that the only differences between pioglitazone and compound b were the replacement of the methyl group by an ethyl group and the location of the ethyl group within the pyridyl ring. *Id.* at 1772.



Grabiak, 769 F.2d 729 [226 USPQ 870]; *In re Lalu*, 747 F.2d 703 [223 USPQ 1257](Fed. Cir. 1984)).

Takeda, 83 USPQ2d at 1174 (emphasis added). Here, the Examiner simply relies on structural similarity with a prior art compound without identifying reasons that would have led one of ordinary skill in the art to make the required modifications. Therefore, the Examiner has failed to meet his burden of proving a *prima facie* case of obviousness. Furthermore, Applicant submits that such reasons are in fact absent from the cited reference, as set forth below.

In *Takeda*, the Federal Circuit found that the accused infringer failed to prove its assertion that the prior art would have selected compound b as a promising compound. The accused infringer argued that one of ordinary skill in the art would have selected compound b as a starting point for modification, and that once selected, the skill artisan would have made two obvious changes, first replace the methyl group with an ethyl group, and then move the position of the ethyl group within the ring to match the position in the commercial compound pioglitazone. *Id.* at 1175.

Compound b was one of 54 explicitly-disclosed compounds in a prior art patent (U.S. Patent No. 4,287,200, "the '200 patent.") *Id.* Additionally, during prosecution of the '200 patent, the applicant submitted results for 9 specific compounds, which included compound b. *Id.* Also available as prior art was a journal article ("the Sodha reference") that disclosed compound b among a total of 101 compounds. The Sodha reference also identified three specific compounds among the 101 disclosed that were deemed most favorable in terms of toxicity and activity. Compound b was not among them. *Id.* On the contrary, the Sodha reference stated that compound b caused "considerable increases in body weight and brown fat weight." *Id.*

Based on the available evidence, the district court found, and the Federal Circuit agreed, that one of ordinary skill in the art would not have selected compound b as a starting compound for modification, even despite the fact that compound b was specifically claimed in a patent that was a continuation of the '200 patent, and despite the fact that during the prosecution of that patent the applicant explicitly singled out compound b as 'specially important' by stating that "the compounds in which these heterocyclic rings are substituted have become important, especially [compound b]." *Id.*

Rather, the district court found that one of ordinary skill in the art would have selected the three compounds identified in the Sodha reference as 'most favorable' and 'valuable for the treatment of maturity-onset diabetes,' as the best 'starting point for further investigation.' *Id.* at 1776-77.

2. *Sternbach* would not have suggested to one of ordinary skill in the art the modification required to arrive at the compounds of the instant invention

A. *Sternbach* does not suggest 3-(2,2-diphenylacetamido)-quinuclidine as a compound useful for modification

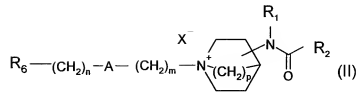
The Examiner bases the instant obviousness rejection on the allegation that *Sternbach* discloses 3-(2,2-diphenylacetamido)-quinuclidine ("Ro 2-3911")[2],and that it would have been obvious to modify Ro 2-3911 to arrive at the claimed compounds. Office Action at 3-4. However, and in analogy with the *Takeda* decision, *Sternbach* fails to identify 3-(2,2-diphenylacetamido)-quinuclidine as a compound suitable for modification. *Sternbach* is principally directed to the esterification of basic bicyclic alcohols with diphenylacetic acid, yielding compounds that do not fall within the scope of

[2] *Sternbach* refers to 3-(2,2-diphenylacetamido)-quinuclidine as "Ro 2-3911" at 2219, col. 1, in the paragraph below the chemical structures.

the instant claims. *Sternbach* discloses that "3-[d]iphenylacetamido-quinuclidine (Ro 2-3911) was prepared from 3-aminoquinuclidine." *Sternbach* at page 2219. However, *Sternbach* does not teach that Ro 2-3911 has any desirable properties that would have motivated one of ordinary skill in the art to choose it for further modification. To the contrary, of the 14 other compounds for which *Sternbach* reports pharmacological testing data for spasmolytic activity, all but one had greater activity than Ro 2-3911, which was over 200 times *less active* than the three most active compounds. *See Sternbach* at page 2220, Table I. Rather than suggesting Ro 2-3911 as a suitable compound for further modification, *Sternbach* identifies three other compounds as being the "most potent compounds" in terms of the desired anti-acetylcholine activity. *Id.* at 2219 (stating that the most potent compounds are Ro 2-3308, Ro 2-3208, and Ro 2-3208; *see also* Table I). Accordingly, one of ordinary skill in the art would not have selected Ro 2-3911 as the starting point for further investigation, but would have chosen Ro 2-3308, Ro 2-3208, and Ro 2-3208 instead. For at least this reason, the Examiner has failed to show a *prima facie* case of obviousness and Applicant respectfully request that this rejection be withdrawn.

B. The claimed quaternary ammonium compounds are more than just a "salt form of the prior art compounds"

As an *independent argument* against the instant rejection, Applicant points out that *Sternbach* neither discloses nor suggests the modifications necessary to prepare the quaternary ammonium compounds of the invention. As recited in rejected claim 33, the quaternary ammonium compounds of the invention have the formula (II):



(II)

Accordingly, the quaternary ammonium compounds of the invention comprise a group R_6-$(CH_2)_n$-A-$(CH_2)_m$- bound to the nitrogen of the quinuclidine ring. Ro 2-3911 is at best a tertiary amine compound with respect to the nitrogen of the quinuclidine ring and *Sternbach* fails to teach or suggest the quaternization reactions that would transform the tertiary amine of Ro 2-3911 into a quaternary amine. Moreover, even if one of ordinary skill in the art would have been motivated to create quaternary ammonium compounds out of Ro 2-3911, which Applicant does not concede, the Examiner has provided no explanation for why one of ordinary skill in the art would have chosen to prepare quaternary ammonium compounds having the R_6-$(CH_2)_n$-A-$(CH_2)_m$- group recited in the claims. Accordingly, not only would *Sternbach* not motivate one of ordinary skill in the art to modify Ro 2-3911 in any way, but it also fails to teach or suggest the specific chemical modifications required to transform Ro 2-3911 into a compound according to the instant claims.

In light of these remarks, Applicant submits that the rejection of claims 33 and 46-49 under 35 U.S.C. § 103(a) is in error and should be withdrawn. Further, Applicant notes that the M.P.E.P. states that "[i]f an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious." M.P.E.P. § 2143.03, citing *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Accordingly, Applicant submits that claims 61-67 are also in condition for allowance.

IV. CONCLUSION

In view of the above amendments and remarks, Applicant respectfully requests reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time not requested elsewhere but required to enter this response, and charge any additional required fees to our deposit account No. 06-0916.

Respectfully submitted,

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Respectfully submitted,

By: 

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